REMARKS

Reconsideration of this application is requested in view of the amendments to the claims and the remarks presented herein. Entry of the amendment is requested under the provisions of Rule 116 as it puts the application in condition for allowance or in better condition for appeal.

The claims in the application are claims 6 to 10, 13 and 14, all other claims having been cancelled. Applicants have cancelled the non-elected claims but reserve the right to file a divisional application directed thereto. It is noted that claim 4 was deemed to be drawn to allowable subject matter.

With respect to the Examiner's request that the specification be amended to refer to the PCT application, Applicants call to the Examiner's attention that this was done in the amendment of May 14, 1999.

Claims 1 to 3 and 6 to 10 were rejected under 35 USC 112, first paragraph, as being based upon a non-enabling disclosure for the scope of the claims as presented and as being based upon a specification that did not demonstrate that Applicants had possession of the invention at the time of filing the application.

Applicants respectfully traverse this ground of rejection

since it is believed that claims 13 and 14 are based upon an enabling disclosure and were clearly within Applicants' possession at the time of filing the application. Claim 4 has been reformulated as new claim 14 and it is believed to be allowable since it is drawn to the SEQ ID No: 2. The new claims 13 and 14 do not protect monomeric protein of the TGF-ß superfamily and each amino acid substitution, as objected to by the Examiner in points 7 and 8, but only to MP52 proteins which have been substituted so that instead of the cysteine which is responsible for dimer formation, one of serine, threonine, alanine or valine is present. The position of the relevant cysteine can be seen from lines 32 to 35 of page 3 wherein it is stated that the cysteine in position NO. 83 is responsible for formation of the intermolecular cysteine bridge and therefore, dimer formation and this cysteine is to be substituted.

MP52 is a well known protein known for a period of time and the active form of which is normally present as a mature dimeric protein. Also for MP52 proteins retaining propeptide parts, activity can be shown as can be seen in WO 97/04095. It is well known that some few amino acid exchanges in the dimeric protein do not influence the activity of the protein. Especially changes and shortening at the N-terminus is not expected to lead to any loss of activity as can be seen from WO 95/04819 and WO 95/16035. The most important part is the beginning of the first cysteine of the conserved cysteine region (position 18 in SEQ ID No: 2). It has to

be assumed that amino acid substitution or changes for which it is known that they are well tolerated by dimeric MP52 also will not lead to a marketed loss of activity in the monomeric form since such substitutions or changes obviously do not have much impact on structure and activity.

The sequence shown in SEQ ID No: 2 (119 amino acids) starts with proline at the N-terminus and is one possible form, although a very preferred one, since during recombinant production of the protein in E.coli, it leads to a uniform N-terminus. Other forms like the naturally occurring mature MP52 with additional alanine (120 amino acids) or with alanine and arginine (121 amino acids) at the N-terminus are comparably active as can be seen by WO 95/04819 and WO 97/04095. The term MP52 protein is intended to encompass such forms of MP52 which have been long known in the state of the art under the proviso that the cysteine for dimer formation is substituted by any one of alanine, valine, serine or threonine.

In this respect, the Examiner's attention is called to the Mason et al citation which only describes monomeric activin A and only refers to monomeric TGF-ß1. Members of the DVR subfamily of the TFG-ß superfamily of proteins which includes BMPs and GDFs (MP52 belongs to the GDFs) are not mentioned in the citation. Mason et al also describes that TGF-ß1 and activin A do not show any or only little activity in the monomeric form. Therefore, this article does not hint in any way of the present invention, namely,

that another member of the TGF-ß superfamily such as MP52 is comparably active in monomeric and dimeric forms. Therefore, this article is in no way relevant to claims 13 and 14 which have been restricted to MP52 proteins.

The claims have been limited not to any amino acid as alleged by the Examiner but to a Markush group of four specific amino acids and they represent a selection of amino acids known that substitution for one another are possible and common in nature. There are amino acids in related proteins of protein families which are exchanged more often than could be expected on a random basis, whereas the exchange for other amino acids is highly unlikely as can be seen from the Dayhoff et al article submitted herewith and especially with respect to Fig. 84 thereof. Using alanine, it could be shown experimentally that cysteine can be substituted in the present application and a possibility for which no success could be expected in light of the prior art (score-2 in Fig. 84), especially since this cysteine is important for the dimer formation. In view of Fig. 84 of Dayoff et al, one skilled in the art had to expect that alanine could again be substituted for another amino acid and the amino acids serine, threonine and valine compared to alanine have a core of 1, 1 and 0. Such scores indicate favorable exchangability and hence, it is obvious that instead that instead of alanine, serine, threonine or valine can be used. Therefore, the specification is enabling and establishes Applicants' possession of the invention as claimed. Therefore,

withdrawal of these grounds of rejection is requested.

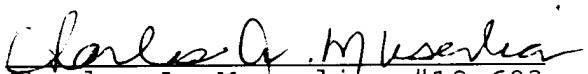
With respect to the rejection of claims 1 to 3 and 6 to 10 as being obvious over the Mason et al reference, Applicants traverse this ground of rejection since as noted above, the Mason et al reference is directed only to monomeric activin A and only refers to monomeric TGF-ß1 which is in no way related to Applicants' MP52 which is active in monomeric and dimeric forms. Therefore, this ground of rejection falls.

With respect to the Examiner's contention that Ngo et al disclose that for the exchange of amino acids at positions which are critical for the protein structure and/or function, some guidance would be needed. This is deemed to be merely a hint that the invention cannot have been obvious. However, in view of enablement, it is shown in the present application that cysteine which is responsible for dimer formation does well tolerates substitutes substitution for alanine although it is a critical position for the structure of the native protein. This critical position unexpectedly can tolerate exchanges and still retain activity and this guidance is definitely contained in Applicants' description in the form of the example since the activity of the protein with alanine instead of cysteine is shown. The fact that also other exchanges can be tolerated at this position is obvious when taking into the general teaching of Dayoff et al for example. With respect to the Examiner's statement that there was no in vivo

examples shown but only in vitro experiments, Applicants will be submitting an in vivo experiment with monomeric MP52 which will be submitted in the form of a declaration in the near future. Therefore, it is believed that Applicants have clearly shown the use of the invention and withdrawal of this ground of rejection is requested.

In view of the amendments to the claims and the above remarks, it is believed that the claims clearly point out Applicants' invention. Therefore, favorable reconsideration of the application is requested.

Respectfully submitted,
Bierman, Muserlian and Lucas

By: 
Charles A. Muserlian #19,683
Attorney for Applicants
Tel.# (212) 661-8000

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Enclosures

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MARKED UP VERSION OF CLAIM 6 SHOWING CHANGES MADE

Claim 6 (amended) An agent comprising the monomer protein [according to any one] of [claims 1 to 4] claim 13 containing an effective amount of the monomer protein for preventing and treating a disease affecting bone and/or cartilage.